PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 91/11136
A61B 5/00	A1	(43) International Publication Date:	8 August 1991 (08.08.91)

(21) International Application Number: PCT/US91/00702

(22) International Filing Date: 1 February 1991 (01.02.91)

(30) Priority data:

474,344	2 February 1990 (02.02.90)	US
473,917	2 February 1990 (02.02.90)	US

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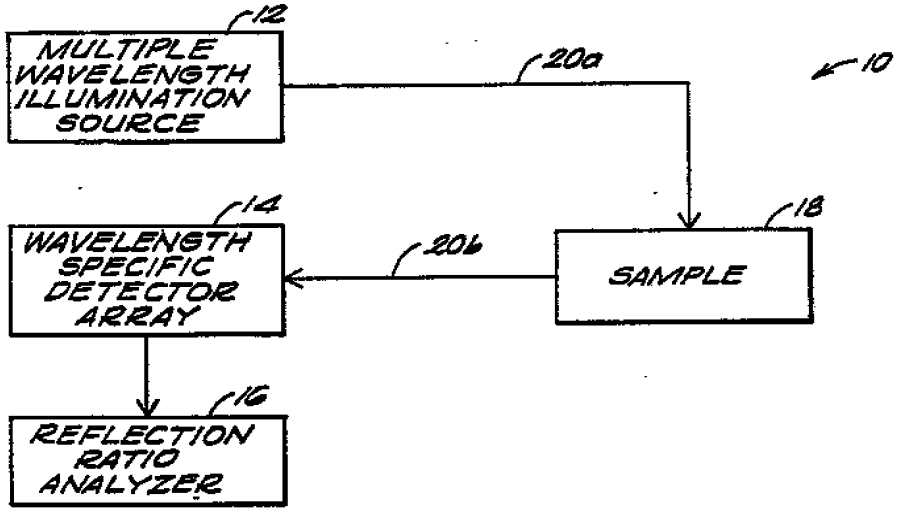
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYSTEMS FOR MATERIAL ANALYSIS BASED ON REFLECTANCE RATIO DETECTION



(57) Abstract

Systems and methods for material analysis are disclosed in which a material is illuminated at a plurality of discrete wavelengths. Measurements of the intensity of reflected light at such wavelengths are taken, and an analysis of reflection ratios for various wavelengths is performed. The present invention permits non-invasive blood analysis by illumination through the skin and similar analyses of meats and other food materials by non-destructive illumination. Changes in the reflection ratios can be correlated with specific material properties such as the concentration of analytes (e.g., oxygen content, glucose levels, cholesterol or drugs) in a subject's circulatory system or the condition of the food material (e.g., oxidation, contamination, sugar content, ripeness, fermentation, degree of cooking, or other processing stages).

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TD	Chad
TG	Togo
US	United States of America

SYSTEMS FOR MATERIAL ANALYSIS BASED ON REFLECTANCE RATIO DETECTION

Background of the Invention

The technical field of this invention is material analysis and, in particular, the invention relates to the detection and quantification of analytes in materials by measuring reflectivity at multiple wavelengths.

Material analysis, especially the analysis of liquid materials for the presence of solutes, can be a tedious and complex task. In many instances it would be more desirable to be able to analyze materials quickly, easily, and non-invasively.

One example of such an application is blood analysis. Treatment of many medical disorders, such as diabetes, requires accurate blood analysis. Additionally, in some situations, repeated or even continuous blood monitoring is desirable, for example, when monitoring drug dosage changes or glucose level variations.

Conventionally, blood is analyzed by withdrawing a sample from the body of a subject and examining it using one or more techniques such as immunoassays, activity assays, chromatographic assays, and spectrophotometric assays. These conventional methods all suffer from several common disadvantages. One disadvantage is that these tests are invasive and raise the risk of patient infection or discomfort. Additionally, such tests are time-consuming. This time delay between when the blood is drawn and when the analysis is completed provides a window during which the subject's blood content may have changed, leading to erroneous test results. A further disadvantage to conventional blood testing techniques is that the people drawing and testing the blood sample are put at risk for exposure to infectious disease agents.

Similarly, the analysis of foods for the presence of contaminants and/or degradation products, can be a tedious and complex task. In many instances it would be more desirable to be able to analyze foodstuffs, such as meats, fruits or vegetables, quickly, easily, and non-destructively. Situations arise when repeated monitoring is desirable, for example when monitoring daily changes in the freshness of refrigerated meats and the like. Similarly, continuous measurements can be desirable in monitoring the cooking or other preparatory steps in food processing.

In the absence of reliable and rapid measurement techniques, wholesome foodstuffs often must be destroyed because arbitrary shelf-life or refrigeration limitations have expired. Likewise, in the absence of careful attention, foods can be ruined due to overcooking or other errors during processing.

Accordingly, it is the object of the present invention to provide an analytic apparatus for non-invasively, quickly, and continuously detecting and quantifying analytes in a material.

It is another object of this invention to provide an analytic apparatus particularly adapted for detecting and quantifying analytes such as glucose in blood in such a way as to avoid the problems of non-continuous test results, subject discomfort, and potential technician exposure to infectious agents.

It is also an object of the invention to provide a system that reduces the number of blood samples which must be drawn from patients who require repeated blood testing to evaluate such parameters as drug dose changes or glucose level variations, and to permit continuous analysis of blood within the circulatory system where desirable.

It is yet another object of this invention to provide an analytic apparatus useful in detecting and quantifying the state or condition of foods.

Summary of the Invention

Systems and methods for material analysis are disclosed in which a material is illuminated at a plurality of discrete wavelengths. Measurements of the intensity of reflected light at such wavelengths are taken, and an analysis of reflection ratios for various wavelengths is performed. The present invention permits non-invasive blood analysis by illumination through the skin and similar analyses of meats and other food materials by non-destructive illumination. Changes in the reflection ratios can be correlated with specific material properties such as the concentration of analytes (e.g., oxygen content, glucose levels, cholesterol or drugs) in a subject's circulatory system) or the condition of the food material (e.g., oxidation, contamination, sugar content, ripeness, fermentation, degree of cooking, or other processing stages).

In one aspect of the invention, an analytic apparatus and method are described employing a multi-wavelength illumination source, a wavelength-specific detector array and a reflection ratio analyzer. The illumination source illuminates a material sample at a plurality of discrete wavelengths at least one of which is selected from the near infrared region. The detector array detects the light reflected from the sample, converts the detected light into electrical signals indicative of the intensity of the reflected light at each wavelength and transmits the converted signals to a reflection ratio analyzer.

The reflection ratio analyzer then derives a reflectance ratio for at least two of the detected wavelengths, at least one of which is selected from the near infrared region, such that the ratio can be compared with predetermined values to non-invasively detect the concentration of analytes in a subject's circulatory system. By performing a ratio analysis, the present invention eliminates background and patient-dependent (e.g., skin pigmentation, thickness, and vascular) factors that might otherwise interfere with accurate measurements.

In one embodiment of the invention, the illumination source further includes at least two laser diodes, producing light at distinct wavelengths, spanning at least a portion of a spectrum from about 500 nm to about 2500 nm, preferably in the near infrared from about 770 nm to about 2000 nm. This embodiment is particularly well-suited to provide a system for detecting glucose in blood circulating through a surface vein due to the penetration of near infrared wavelengths of light through human skin.

One method of the invention utilizes the observation that glucose is relatively non-absorbing of infrared light at wavelengths in the near infrared (e.g., at about 805, 950, 1100 or 1200 nm) and highly absorbing at longer wavelengths in the range of about 1400-2500 nm, in order to determine a blood glucose level from a non-invasive reflection sample.

For example, a surface vein in a human subject can be illuminated with light at about 800 nm to about 1200 nm, and a non-invasive reading is taken so as to establish a baseline serum reflectance value. The vein is also either concurrently or sequentially illuminated with light at a second wavelength in the range of about 1500 to 1700 nm and a second non-invasive reflection reading is taken, so as to establish a blood glucose reflectance level. The ratio of these reflectance readings can be compared to known (e.g., stored in a look-up table) ratios relating to known glucose levels, and a glucose level for the non-invasive sampling thereby determined.

Other blood analytes can be readily detected by selection of other interrogation wavelengths, which preferably provide differential light absorption characteristics for the analyte in question.

The present invention is an improvement over the prior art in that it can non-invasively, quickly and easily detect and/or quantify analytes in blood and other material samples. In this way, the invention eliminates the problems of non-continuous data, subject discomfort and/or potential exposure to infectious diseases.

In another illustrated embodiment of the invention, systems are disclosed for detecting analytes in red meats and other foods, and for monitoring the cooking or other processing steps in the preparation of foods. (As used herein, the terms "food" and "food material" are intended to encompass and include, without limitation, meats, poultry, fish and other seafood, fruits, vegetables, cereals, grains and seeds, dairy products, and beverages as well as food extracts, ingredients, nutrients and/or additives). Measurements of the intensity of light reflected by the food material at such wavelengths are taken, and an analysis of reflection ratios for various wavelengths is performed. Changes in the reflection ratios can be correlated with the concentration of analytes in the food sample.

The invention will next be described in connection with certain preferred embodiments; however, it should be clear that various additions, subtractions and modifications can be made without departing from the spirit or scope of the invention. For example, although the invention is illustrated in connection with a blood and food analysis systems, various alternative embodiments can also be devised, such as systems for monitoring liquid foodstuffs, oils, beverages, chemicals and the like.

Although the illustrated embodiment shows a system with a fiber optic bundle for delivery of six distinct wavelengths of light, it should be clear that the number of interrogation wavelengths, the size and shape of the sampling head and the means for transmitting the light to and from the sample can be varied to meet particular needs and applications. In particular, a single fiber can be used for transmission and detection of multiple interrogation wavelengths. Moreover, although lasers are described as preferred light sources, other illumination means including non-coherent, discrete wavelength light sources can be employed.

Brief Description of the Drawings

FIG. 1 is a schematic block diagram of an analytic apparatus according to the invention;

FIG. 2 is a schematic diagram of the apparatus according to the invention particularly adapted for non-invasive detection of analytes in a subject's blood;

FIG. 3 is a detailed view of the sampling head assembly of the apparatus of FIG. 3;

FIG. 4 is a more detailed illustration of an individual optical fiber and its connection to an illumination source and a detector element according to the invention;

FIG. 5 is a graph of the reflectance spectrum of nonoxygenated and fully oxygenated blood, illustrating the analytical techniques of the present invention;

FIG. 6 is a graph of the reflectance spectrum of glucose, illustrating the analytical techniques of the present invention;

FIG. 7 is a graph of absorbance versus glucose concentration for illumination at 1550 nm and at several glucose concentrations;

FIG. 8 is a graph of reflectivity versus wavelength for a meat sample exposed to air at room temperature overnight, demonstrating the analytical techniques of the present invention; and

FIG. 9 is a similar graph of reflectivity versus wavelength taken at hourly intervals on a meat sample exposed to air at room temperature, further demonstrating the analytical techniques of the present invention.

Detailed Description

A schematic block diagram of an analytic apparatus 10 according to the invention is shown in FIG. 1. Apparatus 10 includes a multiple wavelength illumination source 12, a wavelength specific detector array 14, and a reflection ratio analyzer 16. Illumination source 12 can be a single multi-wavelength laser diode or a series of discrete diode elements, each emitting a distinct wavelength of light. Source 12 illuminates the material sample 18 at a plurality of wavelengths via optical path 20a. Detector array 14 detects light reflected from sample 18 through optical path 20b. The detector array 14 converts the reflected light into electrical signals indicative of the intensity of the reflected light at each wavelength and transmits the converted signals to the reflection ratio analyzer 16 which processes the electrical signals and derives a reflectance ratio for at least two of the wavelengths (at least one of which preferably is selected from the near infrared region). Analyzer 16 then compares the calculated reflectance ratio with predetermined values to detect the presence of an analyte in the material sample 18.

An analytic apparatus 10 according to the invention particularly adapted to provide a system for detecting analytes in blood circulating through a surface vein is shown in FIG. 2. As can be seen from FIG. 2, laser diode elements 12a-12f comprise a multiple wavelength illumination source 12 which provides light at a series of skin penetrating wavelengths (e.g., from about 500 nm to about 2500 nm). Diode elements 12a-12f each transmit a predetermined wavelength of light via corresponding optical fiber elements 24a-24f and sampling head 26, to vein segment 28 of wrist 30. (Alternatively, light at various wavelengths can be emitted by one multiple-wavelength laser diode and transmitted via a single optical fiber.) The discrete wavelengths of laser light automatically pass through the tissue of wrist 30 and illuminate the blood circulating in surface vein 28.

For example, at least one of the diode elements 12a-12f can transmit interrogating radiation in a first wavelength range from about 700 nm to about 1400 nm, more preferably from about 770 nm to about 1200 nm, and most preferably about 800 nm to about 1100 nm. Another of the diode elements 12a-12f can transmit radiation in a second wavelength range from about 1400 nm to about 2500 nm, more preferably from about 1500 nm to about 1700 nm, and most preferably about 1550 nm. In some instances, it may also be preferably to take at least one further reading using another of the diode elements 12a-12f to provide additional baseline data for analyte discrimination (e.g., a reading at 805 nm in order to compensate hemoglobin oxygen concentration changes).

Following irradiation by the diode elements 12a-12f, a fraction of the transmitted light is reflected back from the blood circulating in surface vein 28 along optical fiber elements 24a-24f. (Each optical fiber element 24a-24f carries a reflected light signal having the same wavelength as the light originally transmitted along it.) Diode detectors 14a-14f receive the reflected light from the optical fiber elements 24a-24f and convert these light waves into a series of electrical signals indicative of the intensity of each of the reflected wavelengths of light received from surface vein 28. For example, if laser diode element 12a originally transmitted light of wavelength 500 nm along optical fiber element 14a, then optical fiber element 14a will carry reflected light of wavelength 500 nm back to diode detector element 22a.

As shown in FIG. 2, diode detector elements 14a-14f transmit the electrical signals indicative of the intensity of the reflected light to reflection ratio analyzer 16 along electrical connection 32. Analyzer 16 compares the electrical signals received from diode detector elements 14a-14f to derive a reflectance ratio for at least two of the transmitted wavelengths of light, such that the ratio can be compared to predetermined values to detect the presence of an analyte in the blood flowing through vein 28. Analyzer 16 can also comprise means for quantifying the concentration of the detected analyte.

FIG. 3 shows a more detailed view of the sampling head 26 of FIG. 2. As can be seen from FIG. 3, optical fiber elements 24a-24f of optical fiber bundle 24 are adapted to extend through a corresponding set of holes 32a-32f in the sampling head 26 thus facilitating alignment of optical fiber elements 24a-24f along surface vein 28. Sampling head 26 also comprises taping flanges 34a and 34b located at opposed ends of sampling head 26, providing a means for affixing sampling head 26 above surface vein 28.

FIG. 4 is a more detailed illustration of an individual optical fiber 24a and its connection to an illumination source 12a and a detector element 14a according to the invention. Since each of optical fiber elements 24a-24f is identically adapted, only optical fiber element 24a is shown. Laser diode element 12a is connected to optical fiber element 24a via optical fiber element 36a through optical splitter 38a. Diode detector element 14a is connected to optical fiber element 24a via optical fiber element 40a, also through optical splitter 38a. Optical splitter element 38a (and corresponding elements 38b-38f, not shown) enable dual usage of optical fiber elements 24a-24f so that the light transmitted from laser diode elements 12a-12f and the light reflected back from surface vein 28 travels along the same optical fiber elements 24a-24f.

Laser diodes (or light-emitting diodes) at the preferred wavelengths disclosed herein (e.g., 805 nm, 1100 nm, 1200 nm and 1550 nm) are commercially available from a variety of sources, such as Mastech Int'l. Inc. (Randolph, New Jersey) and/or other sources.

FIG. 5 is a graph of the reflectance spectra of deoxygenated (shown by dashed curve) and fully oxygenated (shown by solid curve) hemoglobin. The wavelength of source light is shown along the x-axis and the intensity of the light reflected back from the hemoglobin is shown along the y-axis. Considering the measured ratio of the reflected light for deoxygenated hemoglobin and oxyhemoglobin at wavelengths of 650 nm and 1000 nm, and referring to FIG. 5, the intensity of the reflected light measured at 650 nm (shown by point A) divided by the intensity of the reflected light measured at 1000 nm (shown by point B) in the case of deoxygenated hemoglobin is less than one. However, in the case of oxyhemoglobin, the same ratio (shown by corresponding points A' and B') is greater than one. Such a clearly differentiable ratio is readily detectable, and the exact ratio can be correlated with the actual oxygen content of the blood sample under analysis.

Similarly, in blood sugar analysis, it has been observed that glucose has peaks in the near infrared that are in well-defined spectral regions and differentiable from the blood background. FIG. 6 is a graph of the reflectance spectrum of glucose. The wavelength of the source light is shown along the x-axis and the intensity of the light reflected back from the blood is shown along the y-axis in arbitrary units. As shown in FIG. 6, glucose shows a strong absorbance peak at about 1550 nm (evidenced by the drop in reflectivity). Furthermore, glucose is essentially non-absorptive at about 805 nm.

These properties of glucose are exploited in the present invention by taking the ratio of light reflected from blood at a first near infrared wavelength from about 770 nm to about 1400 nm where glucose absorption is minimal, and at a second, longer wavelength from about 1500 nm to about 1700 nm where reflectance will be dependent on the concentration of glucose present in the irradiated region.

FIG. 7 is a graph illustrating the principles of the present invention applied to glucose concentration measurement. FIG. 7 is a plot of absorbance of infrared radiation at 1550 nm versus actual concentrations of glucose in an aqueous saline sample. The absorbance measurements were taken by irradiating samples through an excise dog artery wall to simulate <u>in vivo</u> conditions. As can be seen from the graph, the measured absorbance provides an accurate determination of glucose concentration in a linear fashion and over a wide range of concentrations.

While FIGS. 5, 6 and 7 illustrate the invention as applied to detection of oxygen and sugar in blood, in alternative embodiments the invention is suitable for analyzing various other analytes in blood, including cholesterol, insulin, biological factors, and drugs, as well as detecting the components of other materials, such as contaminants in cooking oils, moisture in fuels, alcohol content in beverages, and food adulteration.

For example, with regard to food analysis, FIG. 8 is a graph of the reflectance spectrum of fresh meat (shown by the solid curve) and the same meat sample after exposure to air at room temperature for 24 hours (shown by the dashed curve). The wavelength of source light is shown along the x-axis and the intensity of the light reflected back from the hemoglobin is shown along the y-axis. Considering the measured ratio of the reflected light for the fresh and spoiled meat samples at wavelengths of about 700 nm and about 1200 nm, and referring to FIG. 8, the intensity of the reflected light measured at 700 nm divided by the intensity of the reflected light measured at 1200 nm in the case of the fresh meat sample is substantially greater than one. However, in the case of one day old sample, the same ratio is only slightly greater than one. Such a clearly differentiable ratio is readily detectable, and the exact ratio can be correlated with the actual freshness of the material under analysis. Similar, or in some cases even greater differences are observed in the cooking of meats, particularly red meats.

This same phenomenon of changing reflectance ratios is further illustrated in FIG. 9 where reflectance spectra for a meat sample exposed to air at room temperature is shown at hourly intervals. Again, it can be seen that the peak at about 700 nm drops off rapidly as the sample begins to spoil and a comparison of reflectance ratios at about 700 and 1200 nm yields a reliable and quantitative measure of the freshness of the meat sample.

As indicated above, the invention may be embodied in other specific forms without departing from the spirit or the essential characteristics thereof. The present embodiment is to be considered as illustrative and not restrictive. The scope of the invention is indicated by the appended claims, rather than by the foregoing description, and all changes which come within the meaning and range of equivalent of the claims are therefore intended to be embraced therein.

What is claimed is:

1. An apparatus for detecting an analyte in a material comprising:

illumination means for illuminating a material at a plurality of wavelengths, at least one of which is selected from the near infrared spectrum;

detector means for detecting light reflected from said material at said plurality of wavelengths and for converting said detected light into electrical signals, said signals being indicative of the intensity of said reflected light at each wavelength; and

analyzing means for receiving and comparing said electrical signals to derive a reflectance ratio for at least two of said wavelengths, such that said ratio can be compared with predetermined values to detect the presence of said analyte in said material.

2. The apparatus of claim 1 wherein the illumination means illuminates the material at a plurality of wavelengths spanning at least a portion of the spectrum ranging from about 500 nm to about 2500 nm.

3. The apparatus of claim 1 wherein said illumination means further comprises at least two light sources, each producing light at a distinct wavelength.

4. The apparatus of claim 3 wherein a first one of said sources is operable in the range of about 700 nm to about 1400 nm.

5. The apparatus of claim 3 wherein a first one of said sources is operable in the range of about 770 nm to about 1200 nm.

6. The apparatus of claim 5 wherein said first source is operable at about 805 nm.

7. The apparatus of claim 5 wherein said first source is operable at about 1100 nm.

8. The apparatus of claim 5 wherein said first source is operable at about 1200 nm.

9. The apparatus of claim 3 wherein a second one of said sources is operable in the range of about 1400 nm to about 2500 nm.

10. The apparatus of claim 3 wherein a second one of said sources is operable in the range of about 1500 nm to about 1700 nm.

11. The apparatus of claim 10 wherein said second source is operable at about 1550 nm.

12. The apparatus of claim 1 wherein said illumination means further comprises at least two light sources, producing light at distinct wavelengths of about 1100 and 1550 nm, respectively.

13. The apparatus of claim 1 wherein said analyzing means further comprises means for quantifying the concentration of said analyte in said material.

14. The apparatus of claim 1 wherein the illumination means further comprises means for non-invasively illuminating an in vivo blood sample in a subject and the analyzing means further comprises means to detect and quantify a blood analyte level in said sample.

15. The apparatus of claim 14 wherein the analyte is glucose.

16. The apparatus of claim 1 wherein the illumination means further comprises means for non-destructively illuminating an food sample and the analyzing means further comprises means to detect and quantify the condition of the food such as, for example, oxidation, contamination, sugar content, ripeness, fermentation, degree of cooking, or other processing in said sample.

17. The apparatus of claim 16 wherein the food sample is a meat sample and the analyzing means measures the freshness of the meat.

18. The apparatus of claim 17 wherein the food sample is a fruit sample and the analyzing means measures the ripeness of the fruit.

19. A method for monitoring the composition of a material comprising:

illuminating a material at a plurality of wavelengths, at least one of which is selected from the near infrared spectrum;

detecting light reflected from said material and converting said detected light into electrical signals indicative of the intensity of said reflected light at a plurality of wavelengths;

analyzing said electrical signals to derive a reflectance ratio for at least two of said wavelengths; and

comparing said ratio to a predetermined value to detect the presence of an analyte in said material.

20. The method of claim 19 wherein the step of illuminating said material further includes illuminating said material at a plurality of wavelengths spanning at least a portion of a spectrum ranging from about 500 nm to about 2500 nm.

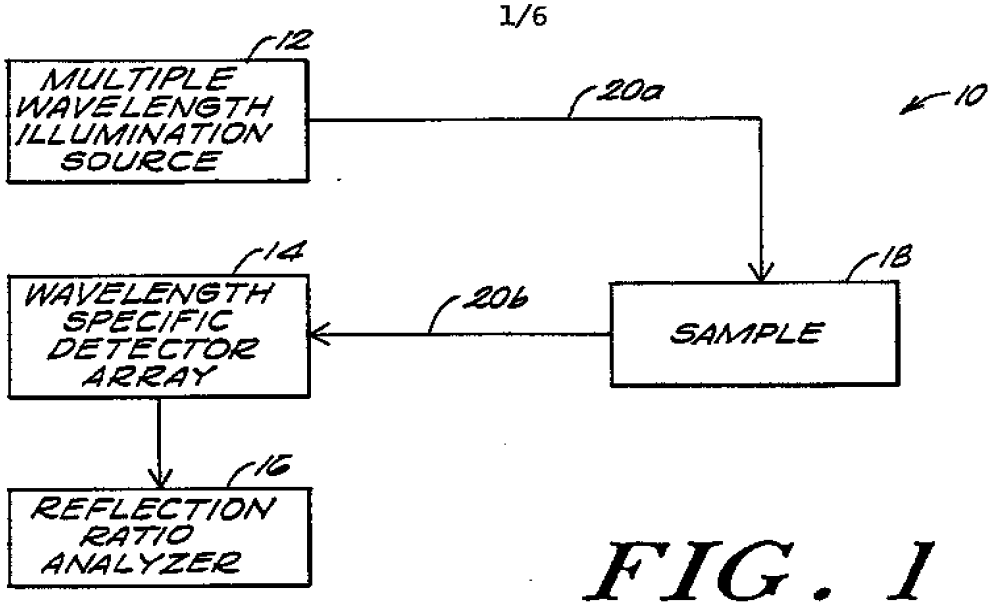
12
MULTIPLE WAVELENGTH ILLUMINATION SOURCE
20a
10
14
WAVELENGTH SPECIFIC DETECTOR ARRAY
20b
18
SAMPLE
16
REFLECTION RATIO ANALYZER

FIG. 1

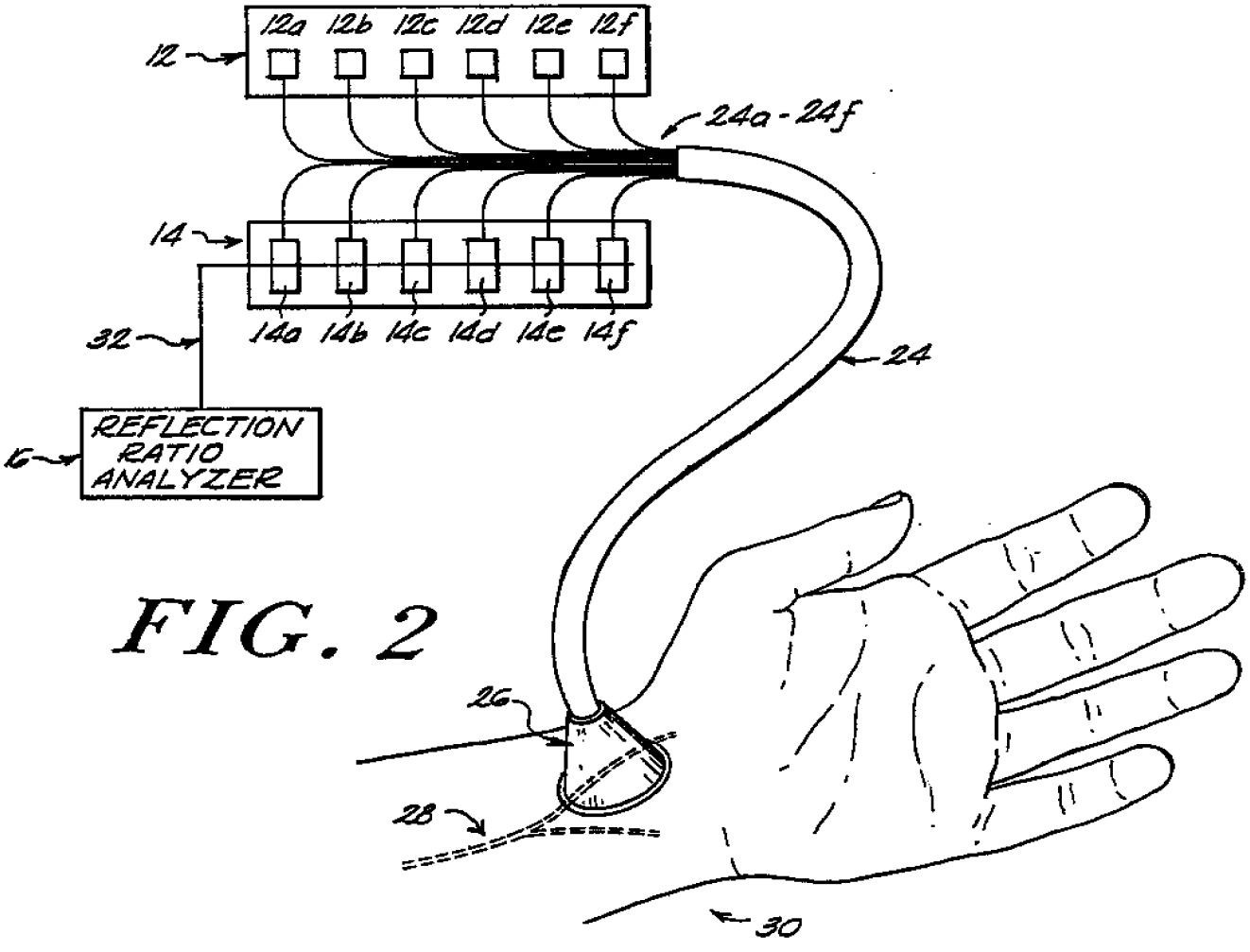
12
12a 12b 12c 12d 12e 12f
24a - 24f
14
14a 14b 14c 14d 14e 14f
32
24
REFLECTION RATIO ANALYZER
16
26
28
30

FIG. 2

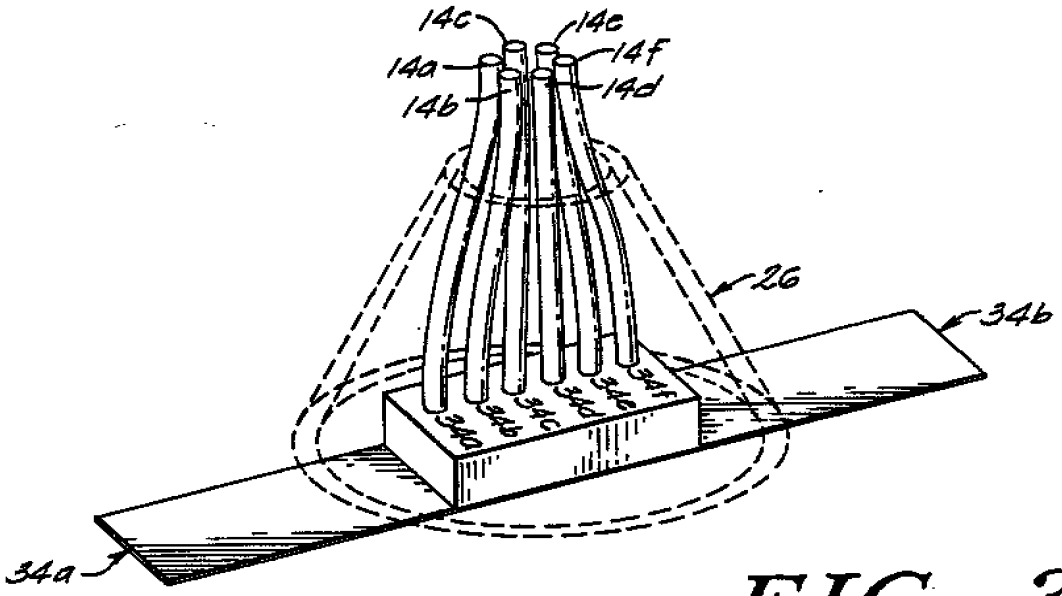
14c
14c
14a
14f
14b
14d
26
34b
34a

FIG. 3

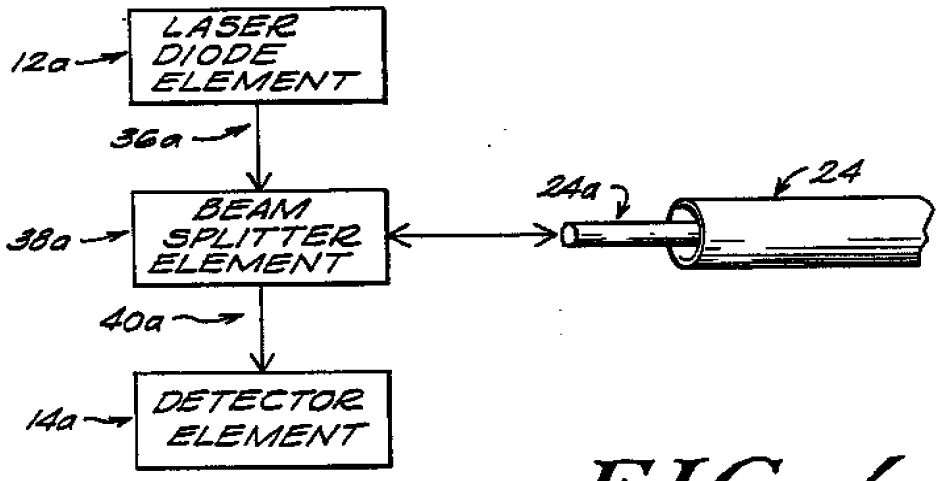
12a
LASER DIODE ELEMENT
36a
38a
BEAM SPLITTER ELEMENT
40a
14a
DETECTOR ELEMENT
24a
24

FIG. 4

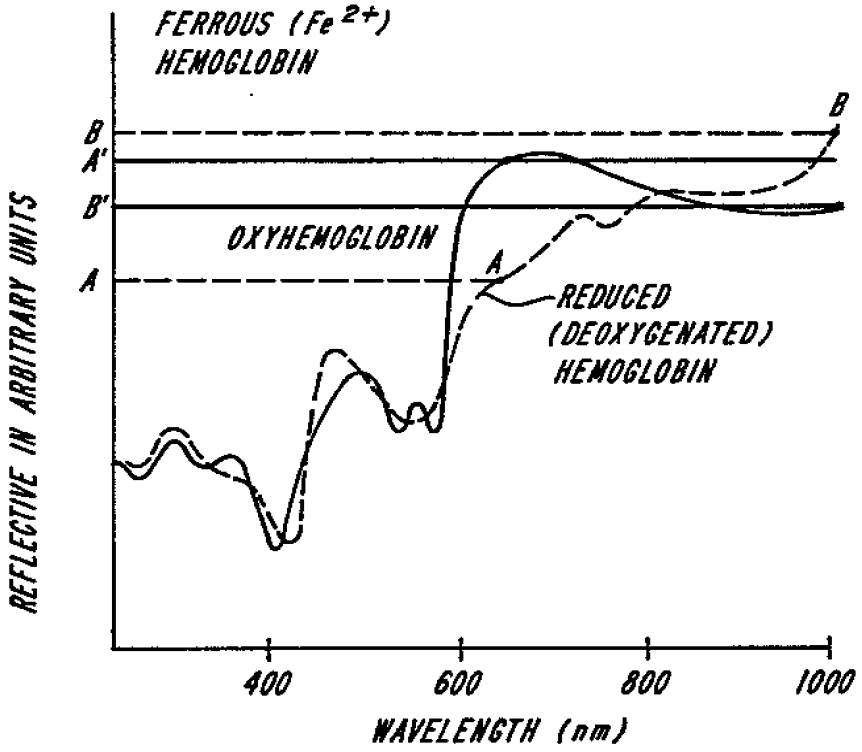
FERROUS (Fe^{2+})
HEMOGLOBIN
B
A'
B'
A
OXYHEMOGLOBIN
REDUCED
(DEOXYGENATED)
HEMOGLOBIN
REFLECTIVE IN ARBITRARY UNITS
400
600
800
1000
WAVELENGTH (nm)

FIG. 5

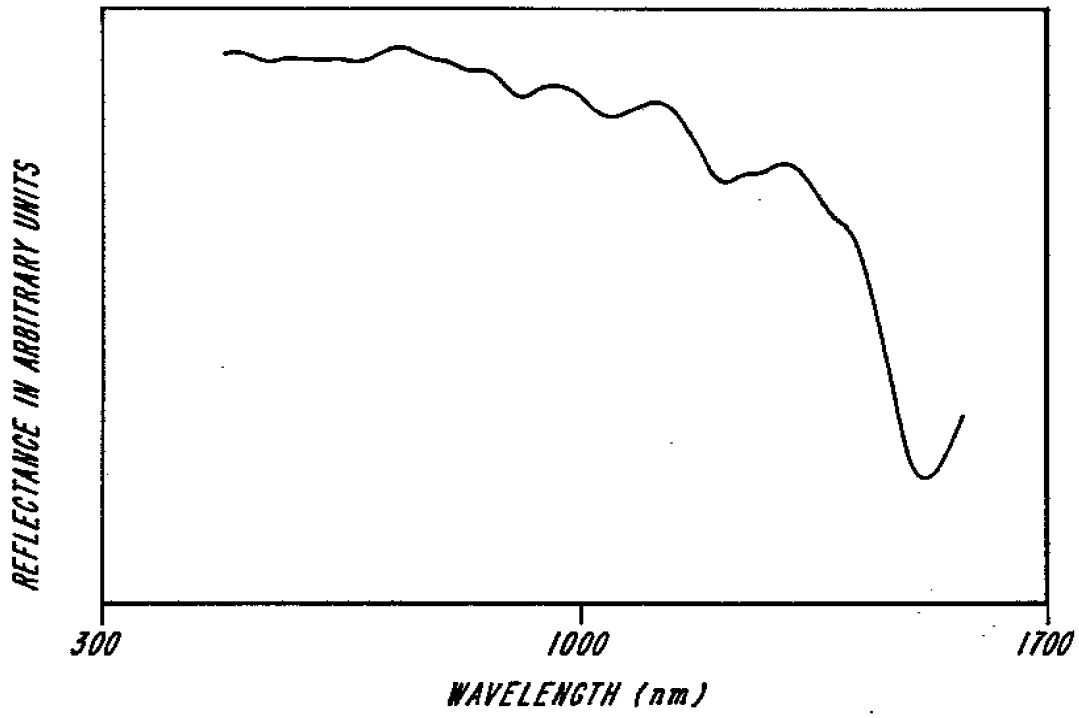
REFLECTANCE IN ARBITRARY UNITS
300
1000
1700
WAVELENGTH (nm)

FIG. 6

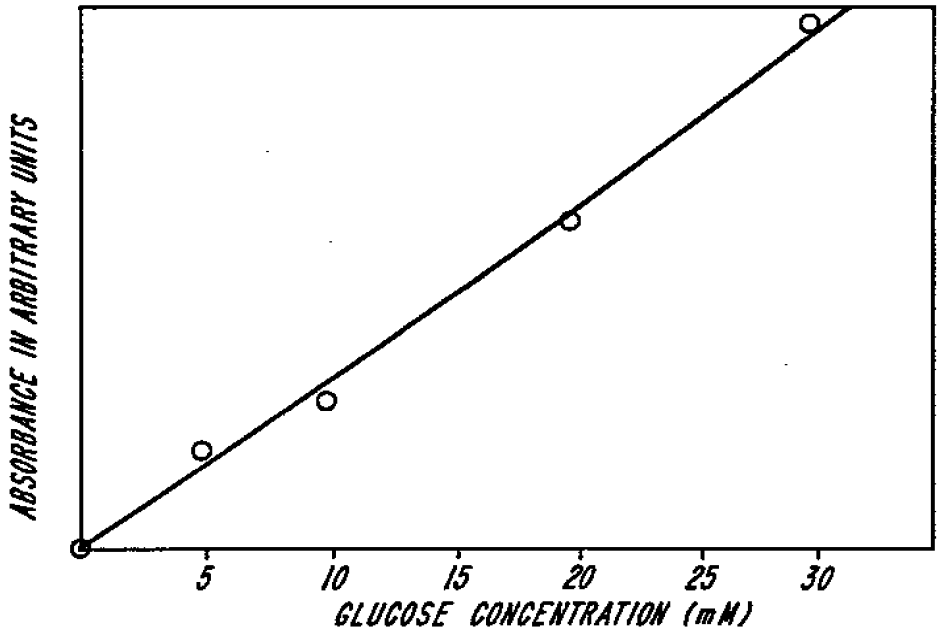
ABSORBANCE IN ARBITRARY UNITS
5
10
15
20
25
30
GLUCOSE CONCENTRATION (mM)

FIG. 7

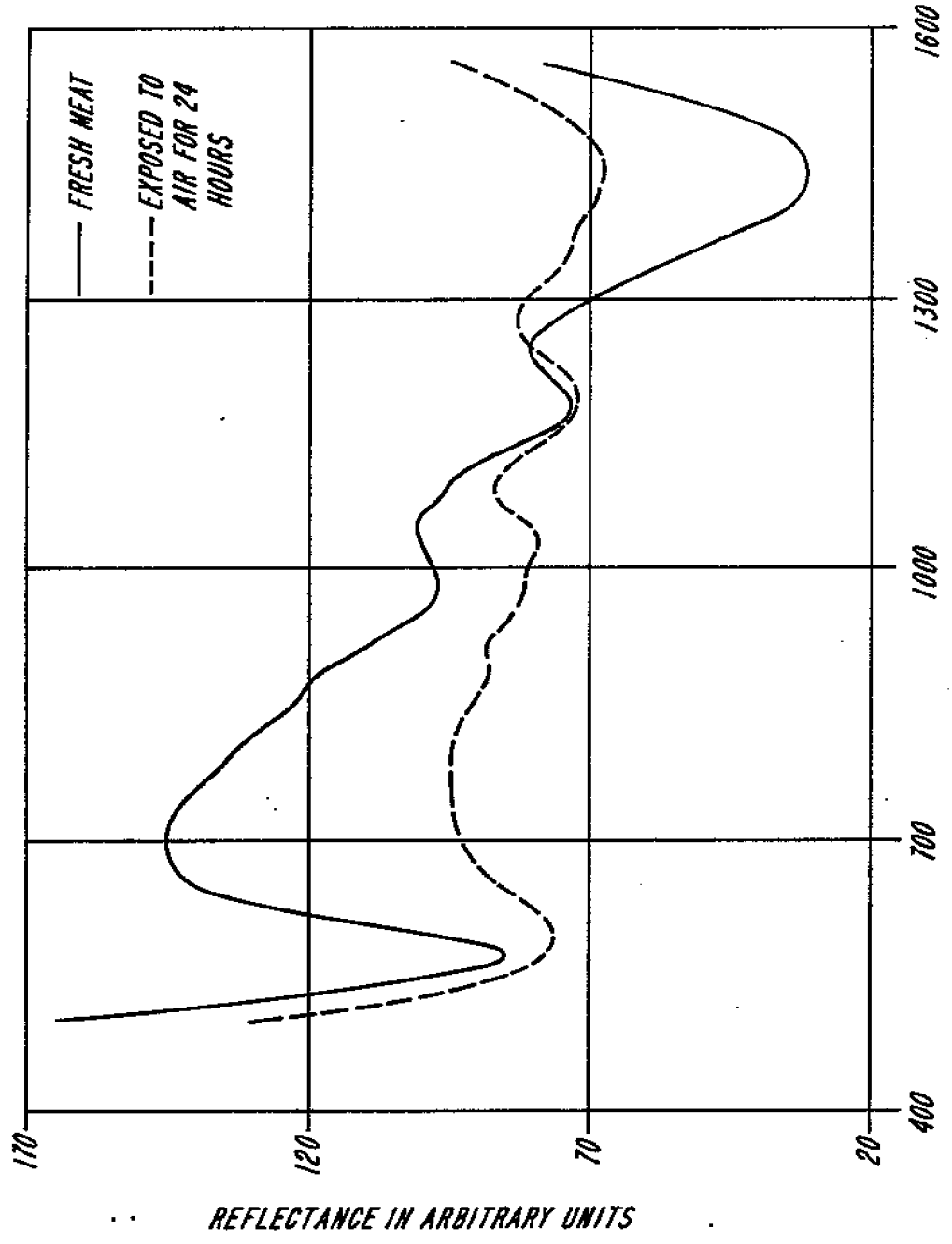
FRESH MEAT
EXPOSED TO AIR FOR 24 HOURS
170
120
70
20
REFLECTANCE IN ARBITRARY UNITS
400
700
1000
1300
1600
WAVELENGTH (nm)

FIG. 8

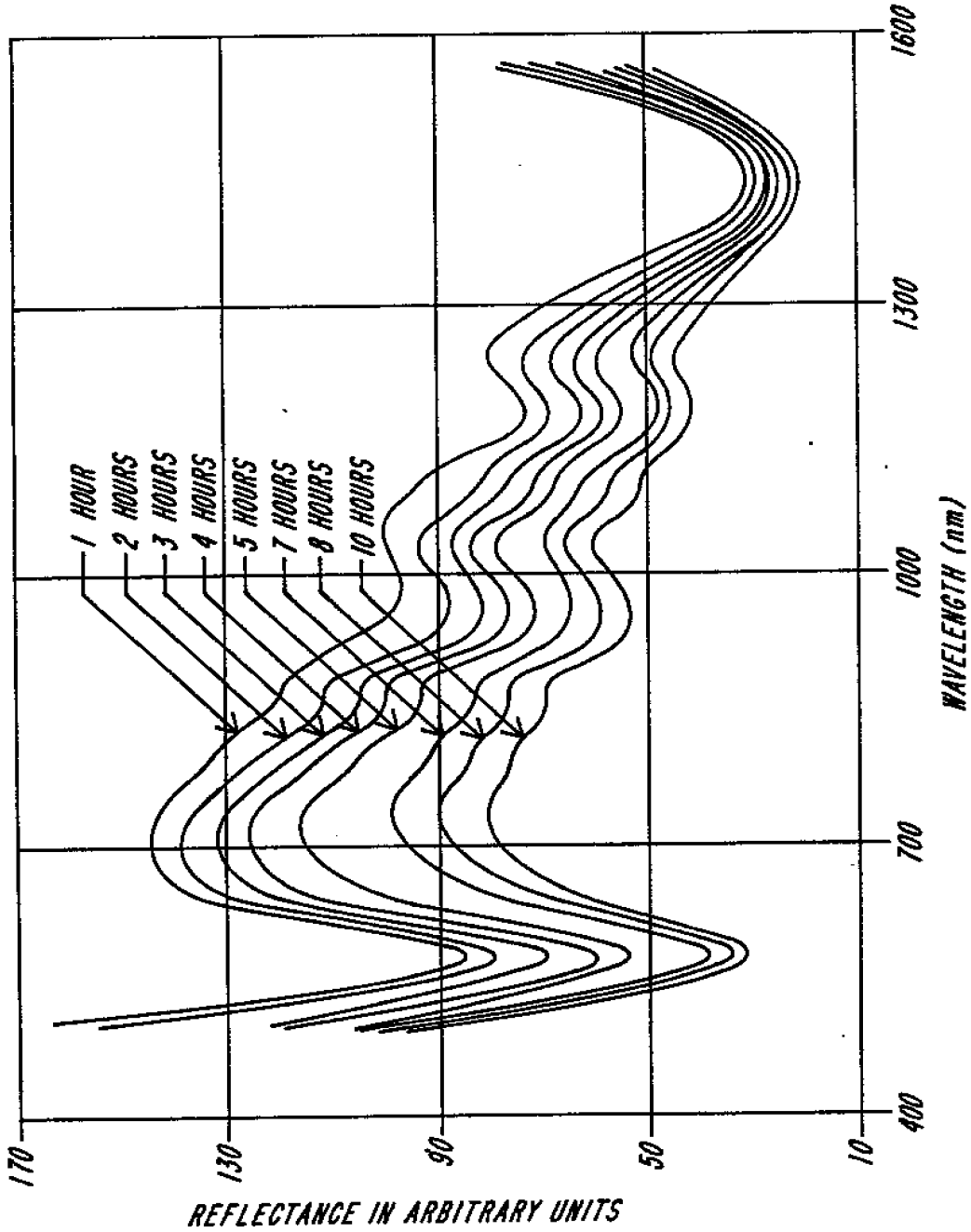
1 HOUR
2 HOURS
3 HOURS
4 HOURS
5 HOURS
7 HOURS
8 HOURS
10 HOURS
1600
1300
1000
700
400
WAVELENGTH (nm)
170
130
90
50
10
REFLECTANCE IN ARBITRARY UNITS

FIG. 9

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,A	EP,A,404562 (UNIVERSITY OF NEW MEXICO) 27 December 1990 see column 15, line 34 - column 18, line 41 see figures 3-5 ---	1-8, 13-15 19, 20

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9100702 SA 44811

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/05/91
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